Clinical Outcome of Patients with Intermediate Probability Lung Scans During Six-Month Follow-Up

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A retrospective review of a consecutive series of patients with intermediate probability (IP) ventilation/perfusion lung scans was performed to evaluate: the frequency of documented thromboembolic (TE) disease, either pulmonary embolism (PE) or deep-venous thrombosis (DVT), at time of presentation; the prevalence of new diagnoses of TE disease during 6-mo follow-up; and occurrence of mortality during the same follow-up interval. Methods: Radiologic and clinical records for all patients who had ventilation/perfusion lung scans reported as IP or indeterminate during a 7-yr period were reviewed. TE disease at presentation or during follow-up was identified from results of pulmonary angiography, chest CT, lower extremity Doppler ultrasound and venography, and repeat lung scans. Occurrence of mortality and cause of death were determined by medical record review. Results: Of 164 patients studied, 36 (22%) had TE disease confirmed at initial presentation (PE = 19; DVT only = 17), and four others (2%) developed evidence of TE disease during follow-up, two with PE and two with DVT. Prevalence of TE disease was significantly greater in patients with matching perfusion/chest radiographic abnormalities and ventilation/perfusion mismatches (0.5–1.5 segmental equivalents) than in those with various patterns of matching ventilation/perfusion defects (31% versus 14%, p < 0.01). Twenty-eight patients (18%) died during follow-up, but recurrent PE was implicated in only one death in a patient with angiographically-confirmed PE at initial presentation. Among the 116 patients who did not receive long-term anticoagulation after their initial lung scans, 22 (19%) died, none of whom had PE confirmed or suspected as a contributing cause. Conclusion: The prevalence of new or recurrent TE disease is low in patients with IP lung scans who are appropriately evaluated and managed after their initial presentation. No evidence of significant mortality secondary to untreated PE was found in the study group.

Key Words: ventilation/perfusion lung scan; pulmonary embolism; deep venous thrombosis; clinical outcome

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The potential morbidity and mortality associated with undiagnosed pulmonary embolism (PE) is a major clinical concern, particularly in light of the nonspecific physical and laboratory findings associated with PE (1–6). The ventilation/perfusion (V/Q) lung scan has a high predictive value for excluding or confirming the diagnosis of PE when the interpretation is normal-to-low probability and high probability, respectively (6–10). However, intermediate probability (IP) lung scans may represent more than one-third of all studies (9), and the appropriate strategy for further investigation and management of patients with this category of scan remains a subject of controversy (10–12). While patients with low-probability lung scans typically have uneventful clinical courses, even though a small percentage will have untreated PE (13–15), the situation for patients with IP lung scans is less clear. Although universal use of pulmonary angiography would resolve the diagnostic uncertainty in almost all patients with IP lung scans (12,16), this approach has not been accepted in clinical practice, as evidenced by the less than 50% angiography rate in most published retrospective series (8,11,17,18). Clinical suspicion (pretest probability) is usually the major determinant of which patients are submitted for angiography, but unfortunately the reliability of such pretest assessment is quite variable (19,20).

This study examines clinical outcomes during the six-month follow-up in patients with IP lung scans, with particular attention to identifying recurrent thromboembolic (TE) disease among those who did not receive long-term anticoagulation. These outcome results were used as an indirect measure of the likely prevalence of clinically-significant untreated PE, in part to determine if a “low probability for clinically significant PE” subgroup could be identified among patients with scans categorized as IP based on commonly used diagnostic criteria (9,21,22).

MATERIALS AND METHODS

During a 7-yr period (1987–1993), 185 consecutive patients with lung scans reported as IP or indeterminate were identified from a review of the reports for the 707 scans performed to evaluate for suspected PE during this interval. For patients studied more than once during this period for the same or similar complaints, only the initial scan was considered in the analysis. Lung scans consisted of a posterior ventilation study performed using 370–1440 MBq 133Xe, followed by an eight-view perfusion lung scan using 185–370 MBq 99mTc MAA containing approximately 200,000–400,000 particles. The higher MAA doses were used in patients who had bilateral radionuclide venography as part of the exam; maximum dose for lung scans alone was 222 MBq. At the time of each original scan reading, a chest radiograph performed within 24 hr was available for review, and interpretations were based on the Biello (21) or the original PIOPED criteria (9).

The classification of each lung scan as IP was evaluated independently by two nuclear medicine physicians without knowledge of clinical course, and a consensus interpretation was reached. As part of the scan review, each scan was classified into one of three general categories based on why it was characterized as IP. These three categories are slightly modified from those originally presented by Biello (21):

A. Matching perfusion and chest radiographic abnormalities of comparable size, with radiographs examined as needed to verify the location and magnitude of abnormalities.
B. One or more subsegmental (moderate size or larger) V/Q mismatches in a region with normal radiographic appearance, with total extent of mismatch not exceeding 1.5 segmental equivalents (9).
C. Extensive lung disease, reflected by significant ventilation abnormalities. This category was further subdivided based on the predominant imaging pattern.

i. Large (multisegment) lung regions with abnormal (diminished or absent) perfusion and xenon trapping.

ii. Marked heterogeneity in perfusion involving at least one lung and diffuse (nontotal) xenon retention.

For studies in which two or more categories were considered applicable, the reviewers reached a consensus regarding the one that reflected the dominant scintigraphic pattern.

As a result of the scan review and later record review, 21 studies were eliminated from further consideration. Four scans with inadequate or absent ventilation studies were deleted, and seven were reclassified as either low (n = 3) or high (n = 4) probability and excluded. In addition, to limit the analysis to patients with suspected new diagnoses and those not already taking anticoagulants, four other patients with documented deep-venous thrombosis (DVT) more than 1 mo before the lung scan also were eliminated. Finally, six patients whose medical records were incomplete or unavailable were excluded. The remaining 164 patients form the population evaluated in this report.

All available medical records for each patient for the 6 mo after the V/Q scan (or until the patient’s death if that occurred during this interval) were reviewed. Information collected included results of diagnostic studies including pulmonary angiography, contrast venography, or lower-extremity Doppler ultrasound, details of hospital course and discharge diagnosis. Only a definitive interpretation of imaging studies as demonstrating PE or DVT was considered positive for TE disease—equivocal findings were recorded as negative. Postdischarge data collected included continued use of anticoagulation, biopsy and/or autopsy results, and imaging evidence of new or possibly recurrent TE disease (DVT or PE). Individuals who had confirmation of DVT or PE only during the follow-up interval were included in the final tabulation for the prevalence of TE disease, on the presumption that this was most likely recurrent disease rather than an unrelated new event.

Statistical comparisons were performed using the chi-square test. A difference at the p < 0.05 level was considered significant.

RESULTS

Of the 164 patients in this study, 156 (95%) were men. Patients ranged in age from 20 to 91 yr (mean, 64 yr). During the 6-mo period after the V/Q scans, 28 patients (18%) died.

Forty patients (24%) had confirmed TE disease (Table 1), with the diagnosis made after the initial presenting episode in 36 patients (22%). Four patients (2%) had objective evidence of TE disease (2 PE, 2 DVT) only during the follow-up period. An additional 10 patients (6%) were treated empirically for PE, usually on the basis of high clinical suspicion and either relative or absolute contraindication to pulmonary angiography or patient refusal to undergo the procedure.

During the follow-up period, six of the 40 patients (15%) with confirmed TE disease died, with one death attributed in part to PE, this in a patient with positive pulmonary angiography who died 2 wk after the lung scan despite adequate anticoagulation and with an autopsy showing progressive pneumonia and old and new PEs. Of the other five patients, three died secondary to pre-existing conditions (cancer —2, coronary heart disease —1), and two died outside the hospital without a definite established terminal diagnosis.

Of the 21 patients (13%) with confirmed PE, the diagnosis was established by pulmonary angiography in 18 patients. One patient had a central PE identified on a chest CT scan. Two other patients had recurrent symptoms and high probability V/Q scans 9 days and 2 mo after the initial IP studies, respectively. Of the 10 patients treated empirically for PE, only one had another suggestive imaging study, an echocardiogram demonstrating a right ventricular clot; five of these patients had negative Doppler studies for DVT.

Twenty-two patients had documented DVT. Nineteen patients had positive Doppler studies initially, including three with angiographically documented PE and one with a positive contrast venogram. One patient had a positive Doppler study 2 mo after the lung scan and one had a negative Doppler exam at the time of the V/Q scan and a follow-up study 4 mo later that demonstrated DVT. One patient had venous and vascular graft thrombosis found at surgery 4 days after the V/Q scan.

Occurrence of TE disease in relation to lung scan categories is shown in Table 1. Confirmed TE disease was significantly more common in patients with scans in Categories A and B than in C (31% versus 14%; p < 0.01).

Among the 41 patients who had pulmonary angiograms, 16 of 28 (57%) patients with Category A or B scans had PE, compared with 2 of 13 (15%) with Category C scans (p < 0.01). Of the 63 patients with venous Doppler studies, occurrence of DVT was similar in patients with A/B or C scans (12/43, 28% versus 6/20, 30%; p = ns). All 10 patients treated presumptively for PE had scans in Categories A or B.

Among the 116 patients who were not anticoagulated with coumadin during the follow-up interval after their initial V/Q scans, four (3%) patients had new or recurrent TE disease, two with PE based on new high-probability lung scans, and two with DVT demonstrated on Doppler exam. The lung scan categories for these four patients were A (n = 2), B and Cii. Twenty-two of the 116 patients (19%) died within 6 mo of the V/Q scan, with six having autopsies. No PEs were found at autopsy, and clinical data did not suggest the presence of TE disease in the remaining 16 patients. Causes of death for these 22 patients are summarized in Table 2.

DISCUSSION

The prevalence of PE in patients with intermediate probability or indeterminate lung scans has typically ranged from 30% to 50% in various published series (8,9,11,18,23–25). In the PIOPED study, prevalence of PE among patients with 1.5 segmental-equivalent V/Q mismatches, still within the IP category, was 72% (26). Despite concerns over the consequences of untreated PE, there remains disagreement concerning the appropriate management of patients with IP scans. While the

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients in V/Q scan category* (Column %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>11 (17)†</td>
</tr>
<tr>
<td>DVT only</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Presumptive PE</td>
<td>7 (11)</td>
</tr>
<tr>
<td>No PE or DVT</td>
<td>42 (66)</td>
</tr>
<tr>
<td>Total</td>
<td>64 (100)</td>
</tr>
</tbody>
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* A: Matching perfusion and chest radiographic abnormalities; B: Ventilation-perfusion mismatches (0.5–1.5 segmental equivalents); C: Extensive lung disease: (i) Multisegment perfusion defect(s) and xenon trapping; (ii) Inhomogeneous perfusion and diffuse xenon retention.

† Also had DVT.
‡ Also had DVT.
results of a decision analysis model suggested that the optimal diagnostic strategy was to obtain pulmonary angiography on all IP scan patients (12), the dominant factor in the analysis was a 30% 6-mo mortality for untreated PE (1), a value that is difficult to confirm clinically and that likely overestimates occurrence of this adverse outcome in current practice (27–29). In addition, it is not reasonable to assume equally severe consequences for all PEs regardless of total clot burden, underlying patient characteristics and risk factors. Follow-up data from patients with low-probability lung scans indicate a generally benign clinical course (13,14). While the relative safety of pulmonary angiography justifies its judicious use when clinical circumstances warrant (30), a better understanding of the clinical course of patients with intermediate probability lung scans also provides valuable insight for judging the necessity for definitively establishing or excluding the diagnosis of PE in these patients.

An original objective of this study was to determine whether there was a “low probability for clinically significant PE” subgroup among patients with IP lung scans as categorized using accepted criteria such as those of Biello (21,22) or the original PIOPED protocol (9). The three categories used in our analysis were derived from those originally suggested by Biello (21), with Category B modified to include larger mismatched defects still within the IP category (9), and Category C subdivided into two commonly observed patterns reflective of obstructive lung disease. Of 164 evaluable patients, 99 had Category A and B scans, of whom 31% had confirmed TE disease, compared to 65 patients with Category C scans, of whom only 14% had TE disease. These retrospective findings support the conclusions derived from the prospective PIOPED study, namely that lung scans with multiple matching ventilation/perfusion defects indicative of obstructive airway or other primary lung diseases, originally classified as intermediate probability for PE at the inception of that trial (9), had in fact a prevalence of PE in the low-probability range (14%) (26). While angiographic confirmation of the presence (or absence) of PE was only available for a minority of the patients in the present series, the follow-up data for Category C patients are consistent with characterization of this group as having a low probability for clinically significant PE or TE disease.

During the 6-mo follow-up, 22 patients who were not anticoagulated with coumadin died, including six on whom autopsies were performed. All deaths were attributable to diseases other than PE. Although it is not possible to exclude the presence of undiagnosed PE in the 16 patients who did not have autopsies, there was no clinical evidence to suggest that a thromboembolic event contributed to these deaths, the majority of which occurred in patients with either progressive malignancy, severe COPD, pneumonia or coronary artery disease (Table 2).

This study has many of the limitations inherent in retrospective review. Whereas the diagnosis of PE or DVT was objectively established or excluded in some patients, clinical follow-up served as the basis for assessing most of those included in the study. As such, the confirmed prevalence of TE disease of 24% can only be an underestimate; inclusion of the 10 patients treated presumptively for PE, for example, increases the prevalence in the study population to 30% (50/164 patients). These prevalence data also include the four patients with PE (n = 2) and DVT (n = 2) only diagnosed during follow-up and assumed to have had undiagnosed TE disease at the time of lung scanning, a plausible assumption in that three of four patients had this confirmed disease within 2 mo of the lung scan. Additionally, as these four patients represent only 2.5% of the study population, their categorization as TE disease positive has only a small influence on the stated disease prevalence, and even if they were categorized differently, the study conclusions would not be significantly affected. The relatively high prevalence of positive angiograms (18/41; 44%) and Doppler studies (18/63; 29%) among the patients who had those exams also indicates a predictable referral bias, with individuals in whom clinical suspicion of TE disease was high being appropriately studied further, while the remaining group of presumably lower likelihood patients had an expected, but perhaps artificially low, occurrence of TE complications during the follow-up interval.

No attempt was made to determine the pretest clinical suspicion for PE in the patients in this review, as it was not considered feasible to reliably ascertain this information from retrospective medical record reviews. Nevertheless, the follow-up data from the patients without pulmonary angiograms or Doppler studies, especially those with Category C scans, suggest that the “low probability for clinically significant PE” subgroup has a similar uncomplicated outcome (from a TE disease standpoint) as has been documented for patients with low-probability scans (13–15). As noted previously, this observation is also in accord with the revised PIOPED study conclusion that lung scans with multiple matched defects, in association with clear radiographs, can be classified as low probability based on angiographic results (26). Similar conclusions were reached in a recent review of a small series of patients with extensive matching V/Q defects consistent with obstructive airway disease, among whom only 4% (1/25) had pulmonary emboli documented on angiography (31).

CONCLUSION

Our findings confirm the appropriateness of the IP category for patients with matching perfusion and chest radiographic abnormalities and those with moderate subsegmental or larger V/Q mismatches (up to 1.5 segmental equivalents). In these patients, follow-up with lower extremity Doppler studies and pulmonary angiograms is warranted to establish or exclude the diagnosis of TE disease. By comparison, V/Q scan findings that reflect primarily airway and pulmonary parenchymal disease (Category C) are appropriately considered as representing low probability of clinically significant or angiographically-prov-able PE. No evidence was found to suggest that untreated PEs resulted in a significant increase in morbidity or mortality in patients with any of the lung scan categories who did not undergo pulmonary angiography and were not anticoagulated with coumadin. Therefore, patients whose lung scans show changes of regional or diffuse obstructive lung disease can in general be managed conservatively without further invasive evaluation. Only in the small number of such patients in whom clinical suspicion of PE is high should pulmonary angiography be considered if lower extremity evaluation for DVT is negative or nondiagnostic.

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ment of Veterans Affairs. Thanks also are ended to Robin Sawyer for her assistance in the preparation of this manuscript.

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8. With the sphincter.
9. Rabbits, nonspecific in 1596.

Scintigraphic Evaluation of Experimental Colitis in Rabbits

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Scintigraphic techniques are frequently used for evaluation of inflammatory bowel disease. The radiopharmaceutical of choice is labeled leukocytes. In this study, two new agents, 111In-labeled polyethylene glycol-coated liposomes and 111In-labeled human nonspecific gamma globulin (immunoglobulin G; IgG), were compared with 111In-leukocytes in a rabbit model of colitis. Methods: In rabbits, acute colitis was induced by colonic instillation of trinitrobenzene sulfonic acid at 25 cm from the anal sphincter. After 24 hr, 15 MBq of the radiopharmaceuticals was injected intravenously in groups of four rabbits. Twenty-four hours after injection, the animals were killed and macroscopic abnormalities were scored in seven consecutive affected colonic segments of 5 cm each (0 = normal, 1 = inflammation, 2 = ulcers). The ex vivo uptake was measured in the normal ascending colon and the affected colonic segments. The colitis index (CI, affected-to-normal colon-uptake ratio) was calculated. Results: Histologically, an acute, patchy, transmural colitis was observed at the site of instillation and the distal colon. The CI of all agents in colitis lesions correlated with the severity of the abnormalities. With increasing severity, the CI for liposomes was 1.88 ± 0.24, 4.88 ± 0.42 and 7.42 ± 0.54 (r2 = 0.68, p < 0.001); for leukocytes 1.77 ± 0.32, 3.10 ± 0.58 and 5.42 ± 0.82 (r2 = 0.31, p < 0.01); for IgG 1.60 ± 0.29, 2.81 ± 0.21 and 2.65 ± 0.21 (r2 = 0.29, p < 0.02). Conclusion: Indium-111-labeled-leukocytes, -IgG and -liposomes all show increased uptake in inflamed colonic tissue. Indium-111-liposomes showed the highest CI, which correlates best with the morphological abnormalities. Indium-111-leukocytes and 111In-liposomes are superior to 111In-IgG for this indication. Key Words: radionucleide imaging; diagnostic imaging; gamma globulin; indium-111; scintigraphy; inflammatory bowel disease

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Inflammatory bowel disease is a condition with fluctuating episodes of relapses and remissions of acute colitis. In clinical practice, diagnostic procedures are most helpful for evaluating the status of the diseased colon. The major diagnostic tools are endoscopy (allowing direct inspection of the diseased mucosa), radiographic evaluation using barium enemas (providing images of the morphological abnormalities) and scintigraphic modalities (showing functional images of the degree of inflammatory activity in affected areas in the gut). For the latter technique, a variety of radiopharmaceuticals are available.

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